NEGLECTED EVIDENCE IN IDIOPATHIC PULMONARY FIBROSIS:

FROM HISTORY TO EARLIER DIAGNOSIS

Perspective

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Abstract

This perspective highlights some evidence that have hitherto been neglected especially because they may not have been sufficiently explicited in the clinical respiratory medicine literature. Idiopathic pulmonary fibrosis (IPF) has appeared only in the second half of the twentieth century and may be, as lung cancer and chronic obstructive pulmonary disease, a direct consequence of the cigarette smoking epidemics. It is a disease of lung aging, with most affected patients being older than 70 years. The relationship between lung aging and pulmonary fibrosis is further illustrated in the bleomycin mouse model, in which older males develop more fibrosis than young female mice.

An earlier diagnosis of IPF is a prerequisite for significant progress to be made in the long-term outcome and prognosis. The present authors consider that only two different yet complementary and realistic approaches could lead to diagnosing IPF earlier and possibly to allowing a more efficient disease management: (i) investigating any patients with early Velcro crackles at lung auscultation through proactive education of - and commitment from – primary care physicians; (ii) and using current large-scale lung cancer screening strategies with low-dose high-resolution computed tomography in smokers for the detection of subclinical interstitial lung disease and especially early IPF.
Idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic interstitial pneumonias, is characterized by extra-cellular matrix accumulation with progressive lung remodelling and eventually honeycomb changes (1). Fibroblasts and especially myofibroblasts play a major role in the production of the extracellular matrix, which mainly consists of collagen (1,2).

IPF occurs especially in men in their sixth and seventh decades, and carries a poor prognosis with a median survival of only 2.5-4 years from diagnosis (3,4). IPF accounts for approximately 20% of cases of interstitial lung disease (ILD) (5). Evidence-based guidelines for the diagnosis and management have recently been published based on extensive literature review (6). However, some evidence has been neglected so far and warrants more emphasis in the respiratory literature.

Here, we especially develop the circumstantial yet strong argument that IPF is a relatively recent disease linked to the tobacco epidemics. We further emphasize that IPF is a disease of ageing, and that earlier diagnosis could be obtained by recognizing the value of Velcro crackles at auscultation and by promoting the screening for IPF as a by-product of low-dose chest computed tomography (CT) screening for lung cancer.

**IPF IS A RECENT DISEASE**

**History of chronic pneumonia**

William Osler has been credited for the description of "chronic interstitial pneumonia" more than a century ago (7). However, interstitial pneumonia did not have the same meaning as it has now. In his book, Osler first stated in the paragraph on morbid anatomy that "the disease
is unilateral" (8), and what he described was indeed the chronic evolution of acute infectious pneumonia rather than an idiopathic fibrotic process. Previous descriptions did not correspond to IPF either. Osler largely referred to Jean-Martin Charcot, who had studied chronic pneumonia in detail, with the sequence leading from acute pneumonia to "pneumonic fibrous metamorphosis" including many "fusiform cells" likely corresponding to (myo)fibroblast (9,10). Wilson Fox (11) comprehensively reviewed in 1871 the literature on chronic pneumonia, and found that two thirds of cases occurred between the age of 15 and 40 years, with acute onset in most cases, frequent hemoptysis, unilateral involvement with retraction of the chest, and fine crepitation at the acute stage that did not persist chronically. Most cases of chronic pneumonia thus likely corresponded to non-resolving acute infectious pneumonia, with probable tuberculosis in other cases (Robert Koch described the eponym bacillus only in 1882). It is critical to notice that despite the careful auscultation of patients by well-trained physicians and the usual practice of autopsy in all large hospitals, there were no reports of a condition consistent with true IPF until the second half of the XXth century.

**Onset of IPF in the Second Half of the Twentieth Century**

Hamman and Rich reported in the 1930s a few patients with fatal “acute diffuse interstitial fibrosis of the lung” (12,13), which was considered an entity close to IPF until the 1960s (14), and is now labelled acute interstitial pneumonia thus differing from IPF (15). It is only from the 1950s that cases of probable IPF were increasingly reported. However, the series reported under the heading of pulmonary fibrosis also included a variety of other ILD, with patients of all ages (including children) (16-19).

In 1968, Averill Liebow proposed a pathologic classification of the interstitial pneumonias that included usual interstitial pneumonia (UIP) (20) that he considered to result from diffuse alveolar damage with hyaline membranes and further interstitial proliferation and
honeycombing. The terminology of IPF especially developed in the 1970s. In 1978, Charles Carrington reported a series of 53 cases of UIP (collected over 25 years) (21), defined as "highly variegated structure often including the entire spectrum from normal alveolar walls to fibrotic, end-stage lesions in the same tissue sample; dense pleiomorphic interstitial cellular infiltrate including many lymphocytes and monocytes but relatively few eosinophils". Fibrosis and honeycombing were considered to be non-specific features of both UIP and desquamative interstitial pneumonia (21). In the following decade, the prevalent concept was that "alveolar macrophages direct the alveolitis associated with IPF", with limited if any role mentioned to fibroblasts (22).

The advent of CT contributed to better characterize the phenotypes of the ILDs. Further clarification resulted from the individualization in the 1990s of idiopathic non-specific interstitial pneumonia (previously mixed with IPF) (23-27), which was definitely acknowledged as a distinct entity only in 2008 (28).

IPF is presently established as a clearly defined entity with precise diagnostic criteria (6,29), with especially a pathology pattern of UIP and characteristic high resolution (HR)-CT features including honeycombing. However its cause(s) remains elusive.

**IPF AS A DIRECT CONSEQUENCE OF THE CIGARETTE SMOKING EPIDEMICS**

The cigarette smoking epidemic started at the end of the XIXth century, and a turning point was the first World War, where cigarettes were provided to soldiers (30). Although lung cancer was very rare during the first decades of the XXth century, statistics around 1930 reported that patients with lung cancer were often smokers. A strong relationship between tobacco smoking and lung cancer already existed and was four times higher for squamous cell
cancer than for adenocarcinoma (31). In 1954, the mortality of British doctors due to lung cancer was demonstrated to rise with the amount of tobacco smoked (32); this landmark study has set the stage for the current era, in which lung cancer has become the most common cause of cancer death worldwide, and the link between tobacco smoking and lung cancer is no longer debated.

Although IPF is strongly linked to tobacco smoking (1,6,33-35), it has not yet been explicitly included in the list of tobacco-associated lung diseases together with lung cancer and chronic obstructive pulmonary disease (COPD) (36-39). The increase in the prevalence of IPF paralleled with some delay that of lung cancer and COPD. Not all patients with IPF are smokers or ex-smokers, however the majority are smokers with a frequency comparable to that found in lung cancer and COPD (e.g. 60 to 80%). Patients with IPF are significantly more likely than controls to report a smoking history with an odds ratio of 1.58 (95% confidence interval: 1.27-1.97) (40), with a possible dose response relationship between tobacco smoking and the risk of IPF (33). Among first-degree relatives of individuals with familial interstitial pneumonia, older age, male sex, and having ever smoked cigarettes are associated with the development of pulmonary fibrosis (41), suggesting that the development of ILD may result from an interaction between age, smoking and genetic factors. These studies were performed before the current international definition of IPF and may have underestimated the relative risk associated with tobacco smoking. Furthermore, disorders resulting from smoking may be associated in a given patient. The syndrome of combined pulmonary fibrosis and emphysema (42,43) strikingly recapitulates the three major respiratory consequences of cigarette smoking, namely pulmonary fibrosis, emphysema, and lung cancer.

The relationship between smoking and pulmonary fibrosis is further illustrated almost experimentally in rheumatoid arthritis. Indeed, tobacco smoking increases the citrullination of
peptides in vivo, fosters the development of anti-cyclic citrullinated peptide antibodies, enhances the risk of developing rheumatoid arthritis with poor response to methotrexate therapy, and increases the risk of developing ILD in the setting of rheumatoid arthritis. Interestingly, UIP is the most common pathologic pattern of interstitial pneumonia in rheumatoid arthritis (44), and has a prognosis similar to that of IPF/UIP (45), further emphasizing the links between tobacco smoking and lung fibrosis.

The fact that IPF developed only from the second half of the XXth century coinciding with the development of cigarette smoking strongly supports the hypothesis that IPF, similar to lung cancer and COPD, may directly result from the epidemics of smoking. Further epidemiologic and pathophysiology studies should be carried on to further confirm this.

**IPF IS A DISEASE OF AGEING**

**Age of Patients**

The median age of patients with IPF is comprised between 65 and 70 years in all series based on current criteria, with a range of 55-80 years (1). In fact, older age (e.g. greater than 70) is the most powerful clinical predictor of the probability of IPF in a patient with idiopathic ILD, while the probability of genuine IPF is extremely low before the age of 50 (46). Although a trend has been reported toward an increase in the incidence and prevalence of IPF, and in the mortality from IPF (47-49), large epidemiologic studies based on precise diagnostic criteria for IPF, are still awaited. It is likely that the increase in life expectancy in western countries partly contributes to the development of IPF in the aging population, however the rise in the burden of disease is not totally explained by this phenomenon (50,51). Specifically, aging of the lung may contribute to modifications of the extra-cellular matrix, increase in the apoptosis
of alveolar epithelial cells, accumulation of mesenchymal stem cells, telomerase dysfunction and shortening and epigenetic changes (52,53), collectively predisposing to IPF and COPD (54).

**Of Young Mice and Older Men**

Surprisingly most animal models of pulmonary fibrosis used young mice to study a condition occurring especially in older men. Support to the concept that IPF may be a disease of lung aging linked to male sex has recently come from experimental studies in rodents. In the past, most experimental studies have been conducted in rodents aged 6 to 12 weeks, the equivalent of about 10 to 12 years in humans(55). A recent study was done with bleomycin instilled intratracheally to young (8-12 weeks) and aged (52-54 weeks) male and female C57BL/6 mice (56). In this model, aged male mice developed more severe lung disease with increased mortality as compared to young mice (56), and young male mice developed more pulmonary fibrosis than young female mice (56,57), demonstrating that both advanced age and male sex contribute to fibrosis pathophysiology in the animal model. Further, mice prone to accelerated senescence are also more susceptible to bleomycin-induced pulmonary fibrosis as compared to control mice (58). These observations collectively suggest that older age and male sex predispose mice to a fibrotic response to alveolar injuries (including tobacco smoking) in a compatible genetic background.

**Pulmonary Fibrosis of Genetic Origin**

In an apparent paradox, familial interstitial pneumonia predominantly occurs at a younger age as compared to non-familial IPF (41). Some clues as to why this may happen has arisen from the recent description of germline mutations in the genes *hTERT* and *hTR* associated to the telomerase complex – a ribonucleoprotein holoenzyme that protects the tips of chromosomes
from “erosion” during cell division - in patients with adult onset of pulmonary fibrosis (59,60).

Mutations in telomerase and telomere genes characterize dyskeratosis congenita, a rare syndrome of premature aging identified a century ago (61,62). About one in five patients with dyskeratosis congenita eventually develops pulmonary fibrosis, and telomerase mutations may be found in about 15% of patients with familial pulmonary fibrosis (59,60,63). Again, a history of tobacco smoking is present in over two thirds of affected patients with mutations (64); current and former smokers have shorter telomeres than age-matched controls (65) including in the alveolar epithelium (66); sex hormones regulate telomerase activity (67) which may contribute to more frequent pulmonary fibrosis in males.

According to the current concept, mutations in telomerase and telomere components predispose to a broad spectrum of disease characterized in adults by pulmonary fibrosis, liver fibrosis and hematologic features (reviewed in (68)), with age of onset and severity determined by telomere length. Although the exact pathophysiologic mechanisms are not known, the loss of telomerase activity may contribute to pulmonary fibrosis through the suppression of fibroblast to myofibroblast differentiation (69) and through alveolar epithelial cell senescence limiting alveolar repair (60,70). Overall, syndromes of short telomeres represent archetypal premature aging syndromes (as illustrated by premature hair graying or hair loss (68,71,72)) and associated to pulmonary fibrosis and squamous cell cancers (especially of the skin, head and neck) (73).

**EARLIER DIAGNOSIS FOR EARLIER TREATMENT OF IPF**
Whereas making an earlier diagnosis of IPF was not a priority in the absence of any effective drug therapy, it has become relevant since recent studies that demonstrated a reduction in the rate of decline of forced vital capacity using pirfenidone (74,75) and nintedanib (76), with further a decrease in the risk of acute exacerbation of IPF for nintedanib (76).

**Delayed Diagnosis**

With the exception of the few presenting with an acute exacerbation, patients with IPF usually follow a course of slowly progressive breathlessness and possible cough, which is underestimated for long by both the sedentary patient and the general practitioner.

The mean duration between first symptoms and referral to a tertiary care center is longer than 2 years (77) and is associated with a higher risk of death independent of disease severity (77). Diagnosing IPF at an early stage is therefore an urgent challenge.

It is likely that some of the delay is due to less attention being paid to clinical examination over the last decades as a correlate to the increasing use of other efficient investigations. Both students and general physicians may further be spuriously discouraged from lung auscultation. The *British Medical Journal* recently published an article where the author wrote "as a student I always agreed that I heard murmurs, crepitations, and rubs, even when I hadn't (…). What I had been taught was highly unreliable (...). Basic auscultation may have value, but (...) crepitation and all other soft signs do not (...). Definitive investigations should be organised on the basis of symptoms irrespective of clinical findings" (78). We strongly disagree with such a provocative and dangerous statement regarding crepitations (crackles) that may contribute to further delay the diagnosis of IPF.

**The value of Velcro crackles for early diagnosis**
We consider that presently only two approaches could realistically allow an earlier diagnosis of IPF: (i) the assessment of “Velcro” crackles by lung auscultation (79) ; (ii) and screening using low-dose chest CT.

The terminology of "Velcro rale" has been coined in 1969 by the Mayo Clinic clinician Richard A. DeRemee (80), who found that "the sound generated by tearing apart mated strips of Velcro adhesive, often used as fasteners on blood pressure cuffs, represents a striking reproduction of the rales of pulmonary fibrosis". Anecdotally, DeRemee later reported (81) the origin of the term Velcro (now a trade mark). The inventor of Velcro had noticed burrs caught in the beard of his goats when back from high alpine Swiss pastures at fall. The hairs were soft as velvet, and the burdock (Arctium lappa) has little hooks when examined under the microscope, hence the word “vel-cro”, from the French velours (velvet) and crochet (hook).

Crackles are almost constant in patients with IPF. Although found in other ILDs and not specific for IPF, Velcro crackles must prompt a thorough diagnostic process, including HRCT of the chest. Crackles may occasionally be heard in healthy individuals especially elderly persons (82), individuals with congestive heart failure, or bronchiectasis, however only rarely are crackles in the latter conditions typical Velcro crackles. In most cases older subjects with Velcro crackles are eventually diagnosed with IPF.

The early presence of crackles before patients are symptomatic and/or lung function is altered has also been reported in conditions where ILD may be expected to develop namely asbestosis (83-85) and rheumatoid arthritis (86). In the absence of honeycombing at HRCT, the diagnosis of IPF requires a lung biopsy (6). This relatively invasive procedure may allow the diagnosis to be made before the disease is too advanced and the lung function too altered for inclusion of the patient into clinical trials or consideration of specific IPF therapy.
Therefore we consider that lung auscultation remains a mandatory step in the diagnostic algorithm of any progressive dyspnea or chronic dry cough, and contributes especially to diagnosing IPF at an early stage, what is a prerequisite for earlier treatment and possibly for improvement of the long-term clinical outcome (79,87,88).

**IPF Screening as a By-product of Cancer Screening**

Low-dose CT of the chest was recently demonstrated effective for lung cancer screening (89). Interestingly, low-dose CT with a new computer aided detection scheme may also detect early ILD (90). Screening for ILD especially UIP has been analyzed as a by-product in subjects (especially smokers) who underwent systematic low-dose CT for lung cancer screening.

Interstitial changes were identified in 80 of 3079 subjects screened for lung cancer, including 7 with honeycombing and 14 with combined pulmonary fibrosis and emphysema (91). In a cohort of 692 smokers included in a lung cancer screening trial, a UIP pattern or other chronic interstitial pneumonia patterns were identified at CT in 2 and 26 patients, respectively (92). In a large study of lung cancer screening, the opportunity to diagnose coronary calcification - which is highly predictive of cardiovascular events and overall mortality – has been mentioned as a by-product, yet surprisingly no reference to IPF was made (93). In a subset cohort of the COPD-Gene study, the prevalence of a chest CT consistent with early ILD varied between 5-10%, with subjects with early ILD tending to have greater exposure to tobacco smoking than those without ILD (94). The incidental finding of ILD at HRCT is also increasingly common (95), as is the identification of subclinical ILD in the setting of familial pulmonary fibrosis (87,96), also contributing to detecting IPF before subjects become symptomatic (79).

We thus consider that in terms of public health, ILD screening should be incorporated as a by-product in any lung cancer screening procedure warranted by a history of smoking.
Honeymoon before Honeycombing

The current IPF guidelines (6) state that the diagnosis of IPF can be made without the need for lung biopsy in subjects with all 4 HRCT features of honeycombing (with or without traction bronchiectasis); subpleural, basal predominance; reticular abnormality; and absence of features inconsistent with UIP pattern (6).

Although honeycombing allows a confident diagnosis of IPF without biopsy, we nevertheless consider that it is unfortunately a sign of already advanced disease. Honeycombing at HRCT (e.g. typical UIP pattern at imaging) is indeed associated with an increased mortality rate as compared to patients with pathologic UIP but no honeycombing on HRCT (97,98). The development in extent of honeycombing on serial CT is associated with shorter survival (99). We suspect that “waiting” for honeycombing to diagnose IPF when early non-specific ILD is present at HRCT may be deleterious to patients who could have undergone a diagnostic lung biopsy earlier with a limited risk, and be treated before lung function is too impaired.

We suggest that a lung biopsy should be discussed during the "honeymoon" of early IPF, e.g. when crackles can already be heard at lung auscultation with only subtle subpleural reticulation at chest HRCT yet lung function is normal or moderately impaired (subclinical ILD).

CONCLUSION

Neglected evidence consists of facts or concepts based on substantial evidence which may be implicit for learned subspecialists but which have not been explicitly formulated and made accessible to a wider audience. The latter was the objective of this Perspective. A final word
is that IPF is a misnomer as it is mainly a consequence of smoking. A better future neutral
terminology could thus be usual pulmonary fibrosis (UPF). Because it is not really idiopathic.
Reference List


